DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Dental and Craniofacial Research

National Advisory Dental and Craniofacial Research Council

Summary Minutes

Date: June 12, 2001
Place: Building 45, Conference Room E1&2
National Institutes of Health
Bethesda, Maryland 20892

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

MINUTES OF THE
NATIONAL ADVISORY DENTAL AND CRANIOFACIAL RESEARCH COUNCIL

June 12, 2001

The 164th meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on June 12, 2001, at 8:30 a.m., in Building 45, Conference Room E1&2, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:30 a.m. to 12:34 p.m., followed by the closed session for consideration of grant applications from 1:30 p.m. until adjournment at 5:00 p.m. Dr. Lawrence A. Tabak presided as Chair.

Members Present:

Dr. D. Walter Cohen
Dr. Samuel F. Dworkin
Dr. Raymond J. Fonseca
Dr. Jay Alan Gershen
Dr. Howard K. Kuramitsu
Dr. Harold Morris
Dr. Linda C. Niessen
Dr. Joan Y. Reede
Dr. Dianne E. Rekow
Mr. Jonathan P. Schuermann
Dr. Martha J. Somerman
Ms. Kim S. Uhrich

Members of the Public Present:

Dr. Aida A. Chohayeb, Professor, Howard University, Washington, D.C.
Dr. Robert J. Collins, Deputy Executive Director, American Association for Dental Research (AADR), Alexandria, VA
Dr. Karl Haden, Division of Educational Policy and Research, American Dental Education Association (ADEA), Washington, D.C.
Ms. Gina G. Luke, Division of Government and Institutional Relations, ADEA, Washington, D.C.
Ms. Pamela Moore, *Capitol Publications*, Washington, D.C.
Dr. Antony Rosen, Associate Professor, Department of Medicine, The Johns Hopkins University, Baltimore, MD
Dr. Eli Schwarz, Executive Director, AADR and International Association for Dental Research, Alexandria, VA
Dr. Van Thompson, Professor, University of Medicine and Dentistry of New Jersey, Newark

Federal Employees Present:

National Institute of Dental and Craniofacial Research:

Dr. Bruce Baum, Chief, Gene Therapy and Therapeutics Branch, Division of Intramural Research (DIR)
Ms. Carolyn Baum, Committee Management Specialist and Council Secretary, Office of Science Policy and Analysis (OSPA)
Dr. Henning Birkedal-Hansen, Scientific Director, NIDCR, and Director, Division of Intramural Research (DIR)
Ms. Karina Boehm, Chief, Health Promotion Branch, Office of Communications and Health Education (OCHE)
Dr. Norman S. Braveman, Associate Director, Office of Clinical, Behavioral, and Health Promotion Research, Division of Extramural Research (DER)
Dr. Patricia S. Bryant, Health Scientist Administrator, Behavioral and Health Promotion Research, DER

Ms. Sharrell S. Butler, Diversity Program Manager, Office of the Director (OD)
Ms. Maria Teresa Canto, Public Health Research Specialist, OSPA
Dr. Lois K. Cohen, Associate Director for International Health, and Director, Office of International Health (OIH)
Mr. George J. Coy, Chief, Financial Management Branch, Office of Administrative Management (OAM)
Ms. Mary Daum, Writer, Public Information and Liaison Branch (PILB), OCHE
Dr. Ray Dionne, Clinical Director, DIR
Ms. Jody Dove, Public Information Specialist, PILB, OCHE
Ms. Brenda Farmer, Program Assistant, OIH
Ms. Christen Gibbons, Computer Specialist, Information Technology and Analysis Branch, OCHE
Dr. Sharon Gordon, Director, Office of Education, DIR
Dr. Kenneth A. Gruber, Chief, Chronic and Disabling Diseases Branch, DER
Ms. Denise Halley, Grants Technical Assistant (GTA), DER
Dr. Kevin Hardwick, International Health Officer, OIH
Ms. Lorrayne Jackson, Diversity Programs Specialist, and Co-Director, Diversity Programs, DER
Ms. Susan M. Johnson, Chief, PILB, OCHE
Mr. William M. Johnston, Consultant, Biomaterials, Biomimetics, and Tissue Engineering Branch, DER
Dr. Dushanka V. Kleinman, Deputy Director, NIDCR, and Executive Secretary, NADCRC
Dr. Eleni Kousvelari, Chief, Biomaterials, Biomimetics, and Tissue Engineering Branch, DER
Ms. Wendy A. Liffers, Director, OSPA
Dr. James A. Lipton, Assistant Director, Office of Training and Career Development, DER
Dr. Yujing Liu, Scientific Review Administrator, DER
Dr. Jack London, Special Assistant to the Director, DIR
Ms. Carol Loose, Budget Analyst, OAM
Dr. Dennis F. Mangan, Chief, Infectious Diseases and Immunity Branch, DER
Dr. J. Ricardo Martinez, Director, DER
Dr. Ruth Nowjack-Raymer, Public Health Research Specialist, OSPA
Mr. Robert Palmer, Senior Research Assistant, DIR
Dr. Yu-Jihng Peng, Fellow, Pain Research, DIR
Dr. Maryann Redford, Health Scientist Administrator, Office of Clinical, Behavioral, and Health Promotion Research, DER
Dr. M. A. Ruda, Senior Investigator, Pain and Neurosensory Mechanisms Branch, DIR
Dr. Martin Rubinstein, Chief, Grants Management Branch, DER
Dr. Ann L. Sandberg, Chief, Neoplastic Diseases Branch, and Director, Comprehensive Centers of Discovery Program, DER
Dr. Vidya Sanker, Fellow, Clinical Research Core, DIR
Dr. Yasaman Shirazi, Scientific Review Administrator, DER
Dr. Rochelle Small, Chief, Craniofacial Anomalies and Injuries Branch, DER
Ms. Cheryl Stevens, Special Assistant for Operations, OD
Ms. Tracy Walker, Secretary, OSPA
Ms. Dolores A. Wells, Program Analyst, OD
Dr. James M. Werffenbach, Staff Scientist, PITA, DIR
Ms. Mary Ann Williamson, Computer Specialist, Office of Information Technology, OD
Dr. Guo H. Zhang, Health Scientist Administrator, DER

Other Federal Employees:

Dr. C. R. Buchanan, Deputy Director for Dentistry, Department of Veterans Affairs, Washington, D.C.
Dr. Bruce Dye, National Center for Health Statistics
Dr. Fred Eichmiller, Director, Paffenbarger Research Center of the ADA Health Foundation, National Institute of Science and Technology, Department of Commerce, Gaithersburg, MD
Dr. Stephen E. Straus, Director, National Center for Complementary and Alternative Medicine, NIH

OPEN PORTION OF THE MEETING

I. CALL TO ORDER

Dr. Lawrence Tabak called the meeting to order. He welcomed all attendees and extended a special welcome to a new ad hoc member of the Council, Dr. Jonathan Schuermann. He asked the Council and other attendees to introduce themselves.

II. REPORT OF THE DIRECTOR

Dr. Tabak highlighted several items from the written Report of the Director (see Attachment III). He commented on the budget, National Research Service Award (NRSA) stipends, and several conferences. On page 1 of his written report, he noted that "at the NIDCR" should be deleted from paragraph 1, line 10.

For fiscal year (FY) 2002, the President's Budget requests $23.1 billion for the NIH, which includes $341.9 million for the NIDCR, an 11.7 percent increase. Congressional hearings have been held on the budget, in the House on May 16-17 and, in the Senate, on May 23. In contrast to previous years, the House held "theme" hearings, on March 28, during which Dr. Tabak participated on a chronic diseases panel, and separate testimony by institute and center (IC) directors was replaced by the sole testimony of Dr. Ruth Kirschstein, Acting Director, NIH. The IC directors were present at both the House and Senate hearings, to respond to specific questions.

Dr. Tabak noted that the NIH is preparing for the "post-doubling" period (post-FY 2003), when the annual budget increase for the NIH is projected to be less than current increases. This anticipated smaller growth has ramifications for NIDCR's flexibility to launch large projects currently and to target research [e.g., through Requests for Applications (RFAs)].

With regard to NRSA stipends, the NIH has announced plans to increase these stipends to $25,000 per year for undergraduates and to $45,000 per year for entry-level postdoctoral fellows. This action was taken in response to the National Academy of Sciences report on "Addressing the Nation's Changing Needs for Biomedical and Behavioral Scientists" and ongoing discussions at the NIH.

Dr. Tabak highlighted several conferences, which the NIDCR has hosted or cosponsored since the Council's previous meeting. An NIH Consensus Development Conference on the Diagnosis and Management of Dental Caries Throughout Life, held March 26-28, resulted in an important finding: that the development of new diagnostic techniques to detect early stages of dental caries may give dentists more options to stop or reverse decay using noninvasive techniques. The full consensus statement from this conference was provided to the Council and is available on the World Wide Web (http://www.ahrq.gov/clinic/dentsumm.htm). On May 7, the NIDCR held its second Patient Advocates Forum, which featured an exchange of information and concerns by 18 patient advocates representing 16 organizations interested in the oral health effects of their respective disorders and conditions. Of particular interest to the participants was a presentation on how to create effective web sites. The Second Annual Entrepreneurial Fair, held February 22 during the World Dental Trade Conference and Expo in Chicago, provided an opportunity for inventors to showcase their discovery or invention. Follow-up surveys are planned to determine which inventions are successful.

On July 30-31, the NIDCR will cosponsor an international conference at the NIH on the Treatment of Salivary Gland Disorders: Alternative Approaches. The goal is to review the state-of-the-art in alternative treatments for xerostomia induced by autoimmune diseases, radiotherapy, aging, and other disorders. Other cosponsors are the National Center for Complementary and Alternative Medicine (NCCAM), the NIH Office of Rare Diseases, the NIH Office of Research for Women's Health, the Food and Drug Administration, and the Department of Health and Human Services' Office for Women's Health.

Details on these and other activities and recent NIDCR scientific highlights are presented in the written Report of the Director (Attachment III).

III. APPROVAL OF MINUTES

The minutes of the Council's meeting on January 22, 2001, were considered and unanimously approved.

IV. FUTURE COUNCIL MEETING DATES

The following dates for future Council meetings were confirmed:

September 24-25, 2001

January 28-29, 2002
June 10-11, 2002
September 26-27, 2002

February 3-4, 2003
June 16-17, 2003
September 18-19, 2003

V. NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Dr. Stephen E. Straus, Director, NCCAM, described the challenges and opportunities for research in complementary and alternative medicine, noting areas of relevance to NIDCR's mission. Dr. Straus was appointed on October 6, 1999, as the first director of NCCAM, which replaced the NIH Office of Alternative Medicine founded in 1992. An expert in clinical research, Dr. Straus also serves as Chief, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases.

Complementary and alternative medicine represents a range of diverse, consumer-driven, largely unproven health modalities. The domains include alternative medical systems such as homeopathy, naturopathic medicine, and traditional Oriental medicine (e.g., acupuncture), mind–body interventions (e.g., meditation, hypnosis), biologically based treatments (e.g., herbal medicines), manipulative techniques (e.g., chiropractic, massage), and energy therapies. Few of these practices have been assessed scientifically as much as acupuncture. Dr. Straus noted, for example, that many studies have been conducted to determine the benefit of acupuncture for acute dental pain. In 1998, an NIH consensus development conference found that there is evidence of acupuncture's efficacy for postoperative dental pain, although its relative efficacy versus conventional analgesia has yet to be determined. Dr. Straus noted that basic researchers have begun to elucidate acupuncture's mechanism of action, that the clinical effects are encouraging, and that the extraordinary scientific results warrant continued investigation.

Estimates indicate that 40 percent of Americans, and more than two-thirds of the world's population, utilize one or more complementary and alternative medical practices. In the United States, this use increased by 30 percent during the 1990s, amounting to approximately $27 billion in out-of-pocket expenses paid by individuals, 60 percent of whom do not inform their conventional physicians and dentists about their use of these practices.

NCCAM was established legislatively in 1998 to conduct and support basic and applied research and research training on complementary and alternative modalities. For NCCAM, the challenge is to build a rigorous research enterprise for the complex, global array of modalities, which are based on anecdotes and advertisements, rather than evidence, and for which product and practice standards are lacking, incentives to manufacturers for developing high-quality, proprietary products are few, advocacy groups are diverse and vested, and scientific traditions are lacking. NCCAM has assumed responsibility for systematically reviewing the hierarchy of scientific data in the field, from anecdotes to case studies to uncontrolled and randomized clinical trials, and to prioritize and support studies of promising modalities related to the NIH areas of emphasis. NCCAM's strategic plan includes investing in research, training investigators, expanding outreach, and facilitating integration with conventional medicine.

Dr. Straus emphasized that NCCAM's capacity to succeed depends on the leveraging of its capital and intellectual resources and interests with the other ICs. Research areas of particular interest to NCCAM and relevant to NIDCR are trigeminal neuralgia, selected estrogen receptor modulators (e.g., soy, pesticides), selected androgen receptor activators, Sjögren's syndrome, and salivary gland disorders. Dr. Straus also noted that, unlike most other ICs, most of NCCAM's research investment is clinically oriented. NCCAM currently supports 16 research centers located throughout the United States. He highlighted, as an example, the Oregon Center for Complementary and Alternative Medicine, which NCCAM solely supports at a cost of almost $8 million over 5 years. The center is founded on a broad collaboration of schools and programs within Oregon Health Sciences University and regionally and involves partnerships of credentialed institutions with more mainstream dental and medical investigators. The three projects under way relate to temporomandibular disorders (TMD)—pain management, randomized comparisons of treatments in women, naturopathic regimens for periodontitis. Two NIDCR Council members serve as consultants to the center.

NCCAM's current activities also include the launching of large phase-III trials in partnership with other ICs, more than 100 exploratory studies, and developmental studies stimulated by 17 RFAs; the training of investigators at all career levels and utilizing all NIH mechanisms of support; the funding of pilot demonstration projects to teach dental and medical students about complementary and alternative medicine; the establishment of an intramural research program; and the broadening of communications, in partnership with the National Library of Medicine, to make 250,000 MEDLINE articles related to complementary medicine from 70 countries accessible to the public. Dr. Straus said that NCCAM's website receives 600,000 "hits" each month. In closing, he noted that NCCAM has received tremendous interest from the complementary medicine community and fantastic cooperation from the other ICs. Since he became director of the center, NCCAM's number of grant applications has increased 16-fold.

Discussion

The Council commended the NIH for "going outside the box" to establish NCCAM and anticipated additional collaborative efforts with the NIDCR. Commenting on NCCAM's potential effect on the use of alternative medicine, Dr. Straus said that NCCAM's intent is to "arm" the public with information to enable individuals to make better decisions about their health care. Two examples of changes in behavior resulting from new information are the decline in use of alternative AIDS treatments when highly active antiretroviral regimens became available and the dramatic decline in use of laetrile following two National Cancer Institute-funded studies showing that the extract was not effective. Regarding the regulation of botanicals, Dr. Straus noted that herbs are highly standardized and regulated in Western Europe, but that a change in U.S. regulations (the 1994 Dietary Supplement Health and Education Act) is not likely in the immediate future. In all of NCCAM's large studies, botanicals are evaluated according to the guidelines for investigational new drugs (INDs), good manufacturing practices, and good clinical practices. Dr. Straus also noted that many health maintenance organizations (HMOs) offer partial or full reimbursement for some alternative medicine services and that, according to a recent survey, this reimbursement is driven by market advantages and state requirements, rather than proven clinical efficacy.

VI. OVERVIEW OF NIDCR'S CHRONIC AND DISABLING DISEASES BRANCH RESEARCH PORTFOLIO

Dr. J. Ricardo Martinez, Director, Division of Extramural Research (DER), NIDCR, presented an overview of NIDCR's chronic and disabling diseases research program. The Institute is providing overviews of its research programs at successive Council meetings. The first overview, presented at the Council's January 2001 meeting, focused on the infectious diseases program. The overviews include presentations on both the extramural and intramural research portfolio.

Division of Extramural Research

Dr. Martinez provided background data on research grant applications and awards by DER's Chronic and Disabling Diseases Branch. This branch's portfolio is the second largest in DER, following infectious diseases, in both total number and amount of awards. In FY 2000, the branch received research grant applications, many from dental schools, totaling more than $25 million. In FY 2000, DER's research grant awards in chronic and disabling diseases totaled

approximately $27 million, to support slightly more than 100 grants. The branch accounts for almost 19 percent of all extramural RPGs, which totaled $146 million in FY 2000.

Dr. Kenneth Gruber, Chief, Chronic and Disabling Diseases Branch, described the branch's program and areas for future development. He emphasized that the program covers a spectrum of areas. Other branches also support awards in the area of chronic and disabling diseases. The five program components are osteoporosis and related bone disorders, TMD, neurodegenerative disorders (i.e., chronic pain), autoimmune diseases, and other systemic diseases. In the past 3 years (FY 1998-2000), the total number of RPGs supported has been fairly steady, with a slight decrease in the total number of R01s, R03s, and R21s and a slight increase in the number of P01s. The total dollars awarded has increased slightly, from approximately $30.2 million in FY 1998, to support 152 RPGs, to approximately $31.7 million in FY 2000, to support 150 RPGs.

To stimulate research in specific areas, the branch has issued a number of program announcements, RFAs, and Requests for Proposals (RFPs), which are currently active. Topics include, for example, receptors and signaling in bone (related to osteoporosis), new approaches to pathogenesis and treatment of orofacial pain, and a cooperative study for autoimmune disease prevention. In collaboration with the National Institute of Arthritis and Musculoskeletal Disorders, NIDCR plans to issue an RFP this summer for a large clinical study of osteoarthritis, including the relation between this disease and orofacial pain. The branch also has supported several conferences and workshops, to focus research on, for example, trigeminal neuralgia, selective estrogen receptor modulators in women, and clinical aspects of Sjögren's syndrome. The branch is organizing NIDCR's participation in the upcoming conference on alternative approaches to the treatment of salivary gland disorders (see section II above).

The branch has identified four main areas for future development, based on current research findings and opportunities. These are bone disorders (e.g., in relation to aging, nutrition, environmental factors, prevention, and targeted drug and genetic treatment); TMD (specifically, use of mesenchymal stem cells to repair the temporomandibular joint); neurochemistry of pain in head and neck cancer (i.e., local neuroactive factors contributing to chronic pain, reorganization of the central nervous system); and disorders of the salivary glands (specifically, development of a family registry and clinical trials for Sjögren's syndrome and mechanisms, prevention, and treatment of non-autoimmune xerostomia).

Division of Intramural Research

Dr. Henning Birkedal-Hansen, Director, Division of Intramural Research (DIR), NIDCR, noted that DIR's program in chronic and disabling diseases is small and complements the DER program. Many of DIR's 35 investigators are involved in pursuing research questions directly related to these diseases. Three areas that are being pursued with more intensity than others are chronic inflammatory disorders (i.e., salivary gland disorders, arthropathies), skeletal defects, and pain.

In the chronic inflammatory disorders area, DIR maintains a major clinical research effort associated with its Sjögren's Syndrome Clinic and supports this effort with an active basic research program focused on salivary gland physiology and innovative, salivary gland-based gene therapy. Dr. Birkedal-Hansen noted that DIR scientists are making progress toward repairing or restoring salivary gland function by gene therapy and anticipate clinical studies in the near future. They also have shown that salivary glands can be used as vehicles for delivering products (e.g., human growth hormone) to other body parts via the bloodstream. DIR scientists also are studying the clinical effects of dental implants in TMD patients and the spontaneous development of arthropathies in genetically altered mouse models. The scientists have found that when proteins of the extracellular matrix are knocked out in genetically altered mouse models, the mice spontaneously develop arthropathies. They are conducting basic biological studies to understand the cellular mechanisms responsible and the beneficial effect they have observed when treating the animals with secretory leukocyte protease inhibitor (SLPI). Dr. Birkedal-Hansen noted that this research has important implications for treatment of TMD, but such studies await development of an appropriate animal model. In response to a question from the Council, he noted that nonhuman primates and pigs are potentially good models for studying TMD, but are not as easy to manipulate genetically as mice.

In the skeletal diseases area, DIR scientists are working to understand both normal and pathological development of bone and connective tissue. These basic research studies are focused on fibrous dysplasia (a noninherited genetic disease), inherited skeletal and dental defects (associated with knocked-out proteoglycans such as perlecan), and growth and use of adult stem cells to form bone, bone marrow, cartilage, stroma, and fat cells. In animal studies, DIR scientists have succeeded in isolating and growing stem cells from blood and in transplanting adult stem cells to form bone and bone marrow, as well as dentin-like structures.

In the pain area, DIR scientists have pursued issues related to both acute and chronic pain for a number of years. Dr. Birkedal-Hansen highlighted three exciting and promising aspects of this research: the plasticity of the nervous system and, particularly, of pain responses (see section VIII below); the application of gene therapy to control chronic pain; and new modalities for imaging the subjective pain response, specifically use of positron electromagnetic tomography (PET) scanning to measure temperature gradients associated with blood flow. DIR scientists also are pursing related research on clinical approaches and palliative care for pain and gender differences in pain.

VI. SJÖGREN'S SYNDROME AS A MODEL OF HUMAN SYSTEMIC AUTOIMMUNE DISEASES

Dr. Antony Rosen, Associate Professor, Department of Medicine, The Johns Hopkins University, Baltimore, Maryland, described the complexity of systemic autoimmunity and the importance of the immune system in systemic autoimmune diseases such as Sjögren's syndrome. He suggested research questions for the future and tools for addressing these questions. Dr. Rosen is an extramural grantee in NIDCR's Chronic and Disabling Diseases program and was attracted to research on Sjögren's syndrome through outreach by NIDCR staff.

Dr. Rosen emphasized three points: (a) systemic autoimmunity is multidimensional in complexity and a major disease problem, making it difficult to study in vivo; (b) despite the complexity of autoimmune rheumatic diseases, they each have very consistent phenotypes, and definition of these phenotypes should be a major focus for future studies; and (c) understanding the role of the immune system, as a neutralizer of complexity and a recorder of disease events, offers insights into the initiation and propagation of diseases such as Sjögren's syndrome.

Dr. Rosen noted that the autoimmune rheumatic diseases encompass a spectrum of disorders with widely varying phenotypes, all characterized by inflammatory damage of tissue and activation of the immune system. Understanding these diseases is complicated because they are genetically heterogeneous, have complex and overlapping phenotypes, are associated with numerous environmental factors, and are kinetically complex, changing over time. Despite these challenges, they can be addressed scientifically because the immune system responds to each of the diseases differently (i.e., with specific autoantibodies) and the disease-specific record of events (e.g., initiation, propagation) for each disease is unique. The specificity of the immune response predicts the biologic phenotype, and the immune system is a "molecular impressionist" in its adaptive response. The "tools" needed to understand these diseases are carefully defined phenotypes, studies of multiple phenotypes across the spectrum of diseases, studies of large numbers of patients, and use of the "power" of the immune system, which gives recognition to structure, is very sensitive to context, and has a large capacity for memory.

Dr. Rosen described his own studies, beginning in the mid-1990s, to apply these tools to better understand lupus. The approach is to define the disease-specific autoantigens, examine the immune response in various clinically appropriate perturbed states, search for circumstances that would initiate this immune response, and address the immune consequences of the identified perturbations in vivo. Focusing on the association between initiation of lupus and sensitivity to sunlight, Dr. Rosen and colleagues irradiated keratinocytes with ultraviolet B light and studied the immune response. The studies demonstrated that autoantigens are clustered and concentrated in apoptotic surface structures. The findings suggest that the apoptotic cell may be a potential immunogen in systemic autoimmune disease and that autoimmune abnormalities may involve a form of apoptosis that differs from the norm and in which rapid, noninflammatory clearance of apoptotic cells is impaired. Dr. Rosen noted that these indications fit well with the concept of dominance and crypticity, which is the major current hypothesis for the pathogenesis of autoimmune disease.

Pursuing studies to define a form of apoptotic death that occurs in non-normal, pro-inflammatory states involving an immune response, Dr. Rosen and colleagues focused on Sjögren's syndrome, the systemic autoimmune disease characterized by inflammatory infiltrates in the salivary and lachrymal glands. The findings of this research suggest that this form of apoptosis may be mediated by granzyme B, a serine protease. Dr. Rosen noted that most autoantigens targeted across the spectrum of autoimmune diseases, including Sjögren's syndrome, are highly susceptible to cleavage at unique sites specifically by granzyme B, a feature that has not been found among non-autoantigens. Continuing studies are focused on understanding the role of the granzyme B pathway in vivo and on identifying other pathways and structures which may be important (e.g., for the 20 percent of autoantigens not modified by granzyme B).

Dr. Rosen encouraged further research on Sjögren's syndrome, a frequent autoimmune disease with significant morbidity and perhaps the best model for understanding systemic autoimmunity. He noted that it shares similarities with most other systemic autoimmune diseases and offers a unique phenotype, measurable outcomes, and access to a relevant target organ. In closing, Dr. Rosen noted other areas for discussion concerning this highly complex group of disorders (e.g., genetic factors influencing target tissues and the immune response, the role of specific antigens in specific tissues, the nature and action of perturbing forces, and the continuance of self-sustaining, propagating forces).

VIII. INJURY, NEONATAL PLASTICITY, AND PAIN

Dr. M.A. Ruda, Senior Investigator, Pain and Neurosensory Mechanisms Branch, NIDCR, described DIR's basic science studies on the organization and development of the nervous system in the presence of persistent pain and tissue injury. In these animal (rat) studies, scientists are focusing on injury as damage to tissue, plasticity of the nervous system in the neonatal period, and pain as a sensory, alerting mechanism to potential tissue injury and damage. Dr. Ruda noted three relevant cues for the development of nociceptive neuronal circuits: growth factors for directing information from the periphery to the central nervous system, use-independent (electrical and chemical) activity, and use-dependent activity (sensory stimulation). The first two cues are most important during the early critical development periods.

Studies in adult (neonatal treated) rats showed that persistent pain and tissue injury during the neonatal period resulted in a significant increase in the density of primary afferents (carrying pain messages) and reorganization of primary afferents at the segmental level. The primary afferents affected appear to be only nociceptors and those associated with growth factors.

Studies of the functional consequences of the altered nociceptive neuronal circuits in adult rats treated neonatally demonstrated an increase in the number of neurons in the dorsal horn that respond to a painful stimulus, with the significant level occurring where the termination of primary afferents is densest. In comparison with adults rats not treated neonatally, the treated rats also exhibited behavioral changes in response to various noxious stimuli, which include a shorter withdrawal time from the stimulus; prolonged reactions (e.g., licking), suggesting changes at the higher centers of the neuraxis; increased electrophysiological activity of individual neurons in the dorsal horn to innocuous, as well as noxious, stimuli; a significantly greater response to heat; and a significant increase in the surface area of the body to which an individual neuron responds.

Dr. Ruda noted that these findings are relevant to humans and have important implications for the care of newborns and infants. The developmental times studied in rats correspond to those in humans (6-month fetus to young child). Analyses indicate that the critical time for the development of altered circuits in rats precedes day 10 postnatally and that the changes occur gradually. Further, pain and inflammation in the periphery during the neonatal period appears to have long-standing consequences for the organization of neuronal circuitry. The neuronal responses and behavioral changes observed in adult rats treated postnatally persisted until at least 12 months of age, the oldest rat studied, which corresponds to well past middle-age in humans.

In summary, Dr. Ruda drew the following conclusions: (a) the increased density of primary afferents carrying pain messages suggests the potential for a heightened response to sensory stimulation; (b) primary afferents which grow into new areas of the nervous system may alter the activity of neurons in these areas; (c) the increased number of neurons responding to pain may be caused by contact with an increased number of primary afferents and/or a reduction in the

number of cells normally lost during development of the dorsal horn; (d) changes may be occurring at higher centers of the neuraxis; (e) persistent neonatal peripheral inflammation results, in adults, in altered response to pain, altered pain behaviors, enhanced central sensitization, increased cellular activity and response to all forms of stimulation at the periphery, and dramatic alteration in pain pathways; and (f) altered pathways may result in plasticity changes that are reflected in unique responses to pain in adults.

Dr. Ruda emphasized the need for adequate management of pain in neonates, based on these research data. She noted that anesthesia was not commonly used in surgical procedures on neonates until the 1980s, but is used currently, especially for major procedures. As technology makes possible surgical procedures in utero, the potential for creating unwanted or unknown alterations in the developing nervous system must be considered and addressed.

IX. CONCEPT CLEARANCE

Dr. Dennis Mangan, Chief, Infectious Diseases and Immunity Branch, DER, presented a concept, entitled "Oral Transmission of HIV AIDS Program," for the Council's information and comment. The NIDCR proposes to issue an RFA to expand research on the oral transmission or the inhibition of oral transmission of human immunodeficiency virus (HIV). As background, Dr. Mangan noted that HIV is transmitted through mucosal surfaces and that transmission through the oral mucosa appears to be very low. Animal and laboratory studies confirm that HIV can be transmitted via the oral tissues. Epidemiological data suggest that risk of HIV infection may be related to oral exposure to HIV, that the relative risk of infection may be increased by trauma or the use of alcohol and drugs, and that the oropharyngeal tissues may serve as an HIV reservoir. In April 1997, an outside panel of experts reviewed the Institute's AIDS research portfolio and recommended that more research on oral transmission was needed. The Summary Report of the Ad Hoc Panel on NIDR AIDS Research was provided to the Council and made available to all attendees.

In response to the ad hoc panel's recommendations, the NIDCR issued two RFAs in FY 1998. Dr. Mangan noted that the applications funded from these RFAs are ending and that the NIDCR wishes to capitalize on the results of this research and to attract new scientists to the field.

With the new RFA, the NIDCR would encourage research in almost all areas of oral transmission and give particular emphasis to studies of the prevention of postnatal transfer of HIV to infants via the oral route, fundamental pathogenic mechanisms associated with oral transmission, entry of HIV into tissues and the role of co-infections and host factors in infection, unique patient populations internationally, and inhibition of oral transmission by oral components and development of substances which could potentially inactivate or inhibit HIV. The RFA would solicit studies on the effects of gender, age, race, and ethnicity on oral transmission.

After a brief discussion, the Council concurred with the concept.

CLOSED PORTION OF THE MEETING

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

X. REVIEW OF APPLICATIONS

Grant Review

The Council considered 368 applications requesting $75,112,036 in total costs. The Council recommended 281 applications for a total cost of $57,339,442 (see Attachment II).

ADJOURNMENT

The meeting was adjourned at 5:00 p.m. on June 12, 2001.

CERTIFICATION

I hereby certify that the foregoing minutes are accurate and complete.

_____	_____
Dr. Lawrence A. Tabak	Dr. Dushanka V. Kleinman
Chairperson	Executive Secretary
National Advisory Dental and Craniofacial Research Council	National Advisory Dental and Craniofacial Research Council

ATTACHMENTS

I. Roster of Council Members
II. Table of Council Actions
III. Director's Report to the NADCRC, June 2001

NOTE: A complete set of open-portion handouts are available from the Executive Secretary.